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Regulatory capacity building and the governance of clinical stem cell research in China

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Abstract

While other works have explained difficulties in applying ‘international’ guidelines in the field of regenerative medicine in so-called low- and middle-income countries (LMICs) in terms of ‘international hegemony’, ‘political and ethical governance’ and ‘cosmopolitisation’, this article on stem cell regulation in China emphasizes the particular complexities faced by large LMICs: the emergence of alternative regulatory arrangements made by stakeholders at a provincial level at home. On the basis of ethnographic and archival research of clinical stem cell research hubs, we have characterized six types of entrepreneurial ‘bionetworks’, each of which embodies a regulatory orientation that developed in interaction with China’s regulatory dilemmas. Rather than adopting guidelines from other countries, we argue that regulatory capacity building is more appropriately viewed as a relational concept, referring to the ability to develop regulatory requirements that can cater for different regulatory research needs on an international level and at home.

Key words: China; regulatory capacity building; regenerative medicine; bionetworks; regulatory orientation

1. Introduction

Stem cell research is hoped to yield knowledge that can translate the regenerative properties of stem cells to stem cell products and therapies. Such regenerative medicine (RM) is expected to extend and heighten the quality of the lives of large numbers of people suffering from old age diseases and protracted and incurable conditions. Critical scientists emphasize the importance of understanding how the cells work in connection with the safety and efficacy of their use (Bianco and Sipp 2014; Bianco 2014). Knowledge of the complexity of the navigation of the cells and their integration into the body are crucial. To maximize safety and efficacy, standards have been developed for scientists to use in their clinical research and applications. However, regulatory standards can both enable and hinder national capacity building, partly depending on a country’s international position: when set high, the cost and expertise required for catering to high standards can disable progress in the field. Such dilemmas have frustrated China’s efforts to reform the national regulation for clinical stem cell research.

This article discusses how some notions of regulatory capacity building imply that it refers to the adoption of international

regulation. International institutions, such as the International Society for Stem Cell Research (ISSCR), tend to assume that regulatory capacity building refers to the ability of countries and institutions to follow ‘international’ regulatory standards. Alternatively, critics of hegemonic regulatory standards have argued for self-regulation at a national and lower administrative level (Sleeboom-Faulkner et al. 2016). But countries that find international regulations unsuitable to their conditions may also experience problems with self-regulation (Wahlberg et al. 2013), due to competing interests and clashing regulatory needs at home. This article uses the example of stem cell regulation in China to illustrate the regulatory dilemmas faced by a large low- and middle-income country (LMIC), as a result of external and internal pressures to follow international regulatory trends, on the one hand, and pre-existing alternative regulatory arrangements made by stakeholders at home, on the other. In this article, we show why such notions are inadequate and how they can be improved upon. We argue that, rather than adopting guidelines from other countries, the notion of regulatory capacity building needs to be regarded in a relational light, and should refer to the ability to address regulatory discrepancies

between the different regulatory needs on an international level and at home.

This article shows that China faces specific dilemmas related to its size, geographical differences in opportunities, diversity in institutional structures, and contradictions between the political centre and peripheral governing institutions. We provide examples of six types of these ‘bionetworks’ of clinical stem cell research: life science research networks that embody regulatory norms, which are shaped in interaction with China’s regulatory dilemmas. The notion of ‘bionetwork’ as used here emphasizes the entrepreneurial nature of productive life science networks that share certain scientific norms and regulatory practices with an appeal to health needs. Their shared activities include networking, lobbying, managing, trading, and collaboration with scientific, governmental, and commercial institutions (Sleeboom-Faulkner and Patra 2011). We will show that a variety of different regulatory orientations have developed as part of these bionetworks, the most common of which we have described in this article. As discussed below, the notion of regulatory orientation refers to the shared normative delineations of ‘good’ and ‘bad’ scientific research and clinical practices underpinning regulatory arrangements in collaborative networks. By illustrating how these norms are related to socio-economic and political conditions, we point out the necessity of adjusting our understanding of regulatory capacity building. As we show below, it needs to have the capacity to deal with a variety of regulatory research needs, both on an international level and at home.

1.1 Standards and regulation

Procedural standards are important to the accurate delineation of the steps that are to be taken when specified conditions of a procedure are met to ensure high quality final products (Timmermans and Epstein 2010). Examples relevant to clinical stem cell research are Standard Operating Procedures (SOPs), and standards and guidelines for preclinical studies, clinical trials, quality controls, Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and external review by independent expert committees. Such regulation is meant to ensure that there is sufficient evidence for the safety and efficacy of the stem cell products. But the conditions under which the various dimensions of procedural standards develop, including exchangeability, ethical acceptability, political authority, financial support, expertise, political pressure, bureaucracy and reputation are crucial to whether and how regulation is embedded in society (Timmermans and Epstein 2010: 72). The development of standards harbours a dilemma: although flexible definitions of scientific objects can be preferable from a research perspective (Fox Keller 1999: 136–41), when it comes to clinical applications, it is important to have procedural standards in place that link quality standards for final products with standards for the characterization of stem cell lines (Sengoku et al. 2011). Thus, a method that reproducibly induces the same differentiated cell lines from different cell lines or cell types can be part of the protocol examined by an institutional review boards (IRBs) or drug regulatory authority.

Although international organizations, such as the ISSCR and the International Society for Cellular Therapy (ISCT), and many countries and regions have developed guidelines, the international, national, and regional guidelines for clinical stem cell research differ substantially and are subject to radical change (Sleeboom-Faulkner

et al. 2016). International authority has been ascribed to the guidelines of the ISSCR (ISSCR 2008) and ISCT (2015), and many countries have followed the guidelines and standards of drug regulatory authorities in the USA and the EU to enable collaborative research efforts. But in LMICs, such as China and India, the articulation of ‘international guidelines’ with local practices has led to sustained regulatory dilemmas. Especially in China, life science innovation is earmarked as a main driver for economic progress, and bioscience and biotechnology have become key areas for government support and funding for scientific research over the last decades (CURE 2009; China National Center for Biotechnology Development 2011; Wang 2011; MoST 2013). Although various sets of regulations for clinical stem cell research and applications have appeared, major gaps and questions regarding research governance remain.

1.2 Regulatory development of clinical stem cell research in the PRC

In China, various sets of regulation have been issued since 2000. Apart from the ‘Drug Administration Law’, issued by the Ministry of Health (MoH, 2001)—now part of the National Health and Family Planning Commission (NHFPC)—the ‘Quality Control Standards for Clinical Drug Trials’ (China Food and Drug Administration [CFDA, 2007] and the ‘Interim Regulations on the Ethical Review of Biomedical Research Involving Human Subjects’ (MoH, 2009), regulation directly pertaining to clinical stem cell science, has appeared in 2009, 2012, 2013, 2015, and 2016 (NHFPC 2016).

In 2009, the MoH promulgated the *Management Measures for the Clinical Use of Medical Technologies*. This regulation classified a range of new medical technologies and procedures into three categories where stem cell transplants were classified as ‘Category 3.’ This category of medical technologies involves serious ethical problems, and safety and efficacy issues that still need to be resolved through clinical trials. The regulation stipulated that clinical applications of stem cell technology had to be halted by 31 October 2009, if they had not applied for or passed auditing (MoH 2009). Although stem cell interventions required MoH approval before clinical application, for-profit clinics and a number of hospitals continued to provide ‘stem cell therapy’.

In January 2012, the MoH issued the *Notification on Self-Evaluation and Self-Correction Work regarding the Development of Clinical Stem Cell Research and Applications* (MoH 2012). It gave stem cell research institutions a period of 6 months for self-evaluation and self-correction, and it announced that the CFDA would not accept any applications until 1 July 2012. Clinical stem cell research and clinical trials came to a virtual standstill in most laboratories and hospitals of academic institutions, although there were exceptions, including military and police academies, private hospitals and some lower-tier academic and medical institutions.

In March 2013, the MoH published three interrelated draft regulations for public comments: *Administrative Measures for Clinical Stem Cell Research Trials*, *Administrative Measures for the Research Base of Clinical Stem Cell Trials*, and *Guiding Principles for the Quality Control of Stem Cell Research Preparation and Preclinical Research* (MoH, 2013). These draft regulations prepared the way to regulation of clinical stem cell research and applications in China (Sui and Sleeboom-Faulkner 2015). It was not until August 2015 that the MoH published the ‘draft’ regulation on clinical

research and applications that involve human stem cells (NHFPC 2015). It affirmed that stem cell technologies would be regulated as pharmaceutical products, with the exception of routine treatment with haematopoietic stem cells. The CFDA published standards and technical procedures for the collection, manufacture, and storage of stem cells for clinical use in the 'Stem Cell Preparations Quality Control and Pre-clinical Research Guidelines' (CFDA 2015); it also specified the required criteria for safety and efficacy assessment in preclinical studies. Only the highest-level hospitals (tier-three) are permitted to conduct stem cell clinical trials. Applications for these trials are to address provincial branches of the NHFPC and CFDA, and, assisted by expert committees, the NHFPC and CFDA jointly review the projects. Clinical trials need to be registered online at the Chinese Medicine Registry and Management System (see Rosemann and Sleeboom-Faulkner 2016).

Despite regulatory efforts, the regulatory framework has not allowed clinical stem cell researchers from state laboratories to formally register new clinical procedures and products (Rosemann 2013). Even after the latest reforms, there are still many unresolved regulatory issues regarding market permissions, international collaboration, 'compassionate interventions', and the implementation of regulatory rules for for-profit and other unauthorized stem cell procedures. Speculations exist about the strategic purpose of regulatory policies in China: some argue that they serve to stop rogue stem cell interventions, while others comment that the half-hearted implementation of regulation aims to allow a wide variety of stakeholder efforts, such as those of private hospitals, companies and military hospitals, to forge ahead with clinical stem cell research (Sipp 2009; Cyranoski 2012). Such policy would have rendered elite laboratories as casualties of strategic deliberation, as their translational research is subject to regulatory oversight through the funding they receive. In this article, however, we are interested in indicating why regulatory capacity building has been such a challenge in China.

1.3 Conceptualization

The regulatory development of many countries is largely influenced by the global dominance of 'Western' research ethics. Various theories emphasize the global hegemony of Western states on life science industry development and regulatory standards (Birch 2012; Salter et al. 2015) through the capitalist exploitation in life science development (Rajan 2006; Cooper 2008; Petryna 2009), the political and ethical governance of RM (Bharadwaj and Glasner 2008; Gottweis et al. 2009; Thompson 2013; Webster 2013;) and 'cosmopolitisation' (Zhang 2012). Such hegemonic conditions could be regarded as disabling, when standards are costly and designs are alien. But not all countries follow Western models. In fact, alternative standards and norms are being developed, and in some countries, a permissive regulatory regime is viewed as enabling (Sleeboom-Faulkner et al. 2016). For this reason, the general focus of global theories on hegemony, neo-liberalism, and cosmopolitanism need to be complemented by a closer examination of how national policies articulate both international and local regulatory orientations in the field of the life sciences. This involves the observation of local modes of stem cell governance, healthcare needs, and economic and scientific ambitions (Sleeboom-Faulkner 2016). In this article, then, we focus on regulatory capacity building defined as the ability to manage and deal with internal and external regulatory pressures on a national regulatory policy-making. We show the challenges faced by a government that has to deal with competing sets of regulations, and argue that these are contingent upon national development

strategies and sub-national economic and political developments in the field.

In our view, there is no single global force and no single local pathway that determines the adoption of regulatory standards and values (Ong and Collier 2008); instead, the particular conditions of a country (Sleeboom-Faulkner et al. 2016) and local regulatory developments form both the limitations and the tools of regulatory capacity building. Rather than view regulatory capacity building as the ability to adopt regulatory standards that are developed and vetted elsewhere, we use the term regulatory capacity building to refer to the efforts of agencies and regulators to find pathways that can organize procedures, formulate guidelines, and meet regulatory challenges by users in practice. However, when harmonized with guidelines of international regulatory organizations, such as the ISSCR, such regulatory capacity building can lead to clashes with and between local stakeholders. Although the regulation may enable the translational research of local elite laboratories, they might clash with local measures taken by existing stem cell networks that work with their own informal regulatory standards. In our view, the regulatory developments that have enabled local economic and technological development in the areas of RM, until recently, have pre-empted the development of what Andrew Barry calls large-scale technological zones (Barry 2006), thereby stymying the development of internationally adjusted regulation.

The harmonization of standards and regulation in stem cell science are believed to enable exchanges in stem cell research and its translation (Eriksson and Webster 2008). In technological zones, such unification takes place in spaces where differences between technical practices, procedures and forms have been reduced or common standards have been established (Barry 2006: 239–45). Technological zones are abstract (not geographical) regions that share a 'community of practice'. The networks in this study, however, are held together and shaped not just by technological knowledge exchanges, but also by entrepreneurial forms of collaboration or bionetworks (Sui and Sleeboom-Faulkner 2015). Such bionetworks develop regulatory orientations instrumental to delineating the rights and wrongs of scientific research and clinical practice. In the case of China, diverging 'local' forms of regulatory harmonization in the field of clinical stem cell research have developed as different communities of practice: diverging spaces of regulatory harmonization have come about across the various bionetworks for a sustained period of time, directly or indirectly supported at various governmental levels. Efforts by the national government to strengthen regulation, aimed at policing and enabling the field, clash with the norms of established communities of practice. In China, this has led to a prolonged regulatory stalemate, frustrating efforts of national harmonization. As we shall argue, this development has been made possible largely due to China's socio-economic and infrastructural diversity, and its political organization: it's relatively large size and power concentration in Beijing have created geographical differences in opportunities; a great diversity in institutional structures has come about, characterized by contradictory developments between regulatory policies created by the political centre in Beijing and those created by provincial governing institutions.

1.4 Method and overview

Regulatory pathways are historical and path-dependent. An emphasis on both regulatory capacity building and the entrenched development of bionetworks is necessary to understand the development of the technological zones that have emerged. Our approach proceeds

from the view that an exclusive focus on how nation states are limited by global hegemonies neglects locally formed hegemonies and the multitude of forms of regulatory orientation that exist at subnational—provincial and municipal—levels. A focus on factors underpinning regulatory development can improve our understanding of national regulatory impasse. This article illustrates the various dimensions of procedural standards using six cases, showing how uneven conditions and the path-dependency of communities of practice yield various orientations vis-à-vis national regulation. The cases were selected to show the contrasting regulatory and working arrangements of stem cell hubs that express a desire for national and workable regulation at national stem cell conferences. Although the cases in themselves are unique, they represent main organized forms of stem cell research in China. The six cases also illustrate a variety of regulatory orientations that have developed in interaction with global regulatory trends and the development of local regulatory arrangements. The notion of regulatory orientation, as pointed out above, refers to the shared normative delineations of scientific research and clinical practices underpinning the regulatory arrangements developed in bionetworks. Examples of such normative delineations are making pro-active regulatory contributions to steer the meaning of what is ‘good practice’, creating alternative regulation to define one’s own ‘good practice’, and toeing the official line to show one adheres to dominant notions of ‘good practice’. The local and institutionally entrenched nature of these diverse regulatory orientations, as we shall see, forms a great challenge to regulatory capacity building on a national level.

The materials presented draw on fieldwork in China, which took place from 2007 and 2014. The authors conducted 128 semi-structural interviews in both Chinese (about three quarters) and English with experts engaged in various aspects of clinical stem cell research (policy-makers and bioethicists [18], company managers and staff [17], stem cell scientists [59], and medical professionals [34]) in over twenty stem cell hubs in Beijing, Tianjin, Hangzhou, Shanghai, Changsha, Wuhan, Taizhou, Shenzhen, Harbin, Haikou, and Guangzhou. In addition, we attended and spoke at various conferences on stem cell science in China and Asia. The relevance of these numbers lies in the broad basis for formulating the six most common forms of regulatory orientation, exemplified by six cases or bionetworks. The interviews were analysed by repeated readings, thematic content analysis, and the abductive method (Timmermans and Tavory 2012) through which we identified as significant examples and explored the concepts of ‘regulatory capacity building’ and ‘regulatory orientation’. As illustrated, the cases exemplifying the bionetworks correlated with various socio-economic and political characteristics. As these characteristics can explain the different regulatory orientations of the bionetworks, we consider them to express the six most common kinds of regulatory orientations.

The eleven cited interviews with scientists working on RM were conducted by the first author in Chinese (9) and English (2). We limited the number of direct references for practical reasons (word count) and to avoid information that can lead to an undesirable identification of interviewees. The names of interviewees (the names shown in the Appendix Table A.1 are pseudonyms), as the focus of this article is on institutional processes rather than on persons. However, when we draw on materials on well-known figures that can be found in the public domain, we have copied the names used in the publications concerned. We have made sure that the connections relating our interviews to these publically known individuals cannot be traced.

The next section introduces six bionetworks, followed by a discussion of regulatory orientations and why the notion of regulatory capacity building needs to be relational in order to be effective (Table 1).

2. Bionetworks and the formation of technological zones

The bionetworks described in this section exemplify the most common types of communities of clinical stem cell research practice and have developed their own regulatory orientation. As discussed below, the locally entrenched bionetworks develop particular ‘technological zones’ across geographical boundaries. This makes regulatory harmonization particularly challenging.

2.1 Beijing’s Chinese academy of medical sciences: elite institutions close to power

The case of the Chinese Academy of Medical Sciences (CAMS) exemplifies a bionetwork close to central power. It relies heavily on state support, and illustrates how the state has affected its standards of protocol creation, safety, and efficacy. CAMS is a leader in immunology, and pioneers foetal stem cell research (Eurekalert 2009). Professor Zhao Chunhua leads research on clinical applications of haematopoietic stem cells, complemented with what are controversially known as bone marrow-derived mesenchymal stem or stromal cells (BM-MSCs) (cf Bianco 2014). Zhao was the first in China to receive support from the State Food and Drug Administration (SFDA) (the current China Food & Drug Administration [CFDA]) to start a clinical trial for patients with graft-versus-host disease (GvHD).

In 2003, when Zhao first asked permission to use BM-MSCs in a clinical trial, no clear guidelines were available for the use of allogeneic cells, defined by the CFDA as Grade-3 new drugs in need of research review. Zhao’s group provided regulators with basic explanations of the procedures, and helped create the regulation that gave them permission to go ahead with the BM-MSCs trial in patients with GvHD in 2004 (interview Cha, also see Chen 2009). In December, Zhao began to collaborate with another CAMS team in Tianjin, which had access to patients in the People’s Liberation Army (PLA) 307 Hospital (People’s Daily 2005). In 2006, Phase II of the GvHD clinical trial commenced, but in 2009, when Phase II was close to finishing, the then-SFDA put a general halt to clinical stem cell applications. Nevertheless, Zhao was able to continue recruitment for clinical trials for biliary cirrhosis (ClinicalTrials.gov 2016a), and for GvHD, in collaboration with CAMS, Zhejiang University and various military hospitals, which are regulated separately (ClinicalTrials.gov 2016b). In 2012, Zhao’s study was the first ‘pilot’ case to get permission to conduct clinical trials to test the new regulatory system (interview Cai).

Being an elite institute close to the corridors of power has shaped the regulatory orientation of CAMS through both its dependence and influence on state power. Thus, it has received substantial state support. For instance, in 2004, the Ministry of Science and Technology (MoST) invested some 40 m RMB (then US\$ 4.8 m) into the research (People’s Daily 2005; Chen 2009). At the same time, it could help create the regulation from which its own research would benefit, and it had access to a network of hospitals and state supported academies. Most elite laboratories of well-known academies and universities receive state funding through which they are tied to state policies. Such elite laboratories usually develop a regulatory

Table 1. Bionetworks, example, and their regulatory orientations

Bionetworks	Example	Regulatory orientation
1. Elite institutions close to main regulatory power hubs	CAMS, Beijing	Positive regulatory orientation vis-à-vis official guidelines
2. Stem cell industries straddling elite research institutes and private companies	Tianjin	Multiple regulatory orientations
3. Military stem cell hubs	Various	Independent regulatory orientation
4. Large-scale Commercial Cell Banking and Processing industry	Beike Biotech	Double regulatory orientation
5. Regional university-hospital-industry alliances away from Beijing	Guangzhou Alliance	Split regulatory orientation
6. Enterprises partly dependent on the (distant) state—partly privatized	Xiangya, Changsha	Compliant regulatory orientation

orientation of toeing the official regulatory policy-line. However, by being so close to state power, this bionetwork was able to work proactively by contributing to regulatory developments.

2.2 The Tianjin's stem cell cluster: stem cell industries straddling elite research institutes and private companies

The entrepreneurial cluster around Tianjin Municipality exemplifies the hybridization of state-supported higher educational institutions that have been able to attract private funding. Such clusters combine funding received from state institutions, local governments, and private companies. Their institutional complexity provides them with the leverage to carve out developmental pathways that are not always supported by the central government. The hybrid cluster illustrates the state's challenges of implementing national standards of safety, efficacy, and ethics. In 2000, Tianjin set up the National Stem Cell Engineering (NSCE) Industrialization Base, where its research centre developed a technological platform (2002), which was to serve the development of the life sciences. Professor Han, a successful scientist who spent 11 years in Paris, was asked to run the famous Institute of Hematology (IH) of the Chinese Academy of Medical Sciences (CAMS) /Peking Union Medical College (PUMC). The IH has received major funding from the state (IH 2014), and from private sources for the construction of buildings in the TEDA development zone. Han co-created the company Union Stem Cell & Gene Engineering (USCGEN), and, together with Zhao Chunhua set up the Tianjin Umbilical Cord Blood Bank in 2001. The local government invested over 10 billion RMB in the Tianjin Huayuan Hi-tech Park, where the Tianjin UCB was established. Claiming to meet international standards, it obtained a license from the MoH (IH 2014).

Under Han's direction, 50-odd hospitals in Tianjin started sending umbilical cord blood (UCB) to the bank. Now USCGEN manages and owns the entire process of UCB collection and research: recruitment, banking, cryopreservation, clinical application of stem cells, R&D, manufacture, and the distribution of monoclonal antibodies and gene chips. In June 2002, USCGEN set up the University for Pregnant Women to persuade couples to donate UCB (Union Stem Cell 2014). With the support of the National Development and Reform Commission and the Tianjin City Government, the Cell Product National Engineering Research Center was set up in 2004. In the same year, however, Han used his shares from USCGEN to establish Tianjin Amcell Gene Engineering Co., Ltd., producer of human UC-MSCs, adipose-derived MSCs, placenta-derived MSCs, and amniotic membrane-derived MSCs. Its projects are financially supported by Tianjin City, and backed by research in the IH. In January 2007, Han also set up Hanshi or Huaxia Ganxibao Lianmeng (translated as 'The Beijing Health and Biotech Group'),

which specializes in placenta UCB banking (HanShi 2011). In 2008, Tianjin City UCB Bank and the China Bone Marrow bank linked up with Tianjin Xiehe hospital, which was opened in May 2007, and started to specialize in stem cell transplantation and genetic diagnosis in 2008. It has become a large-scale centre for stem cell storage, research, and applications (interview Li).

While receiving considerable state funding for the IH and the Cell Products & National Engineering Research Centre, Han's network was mainly indebted to local investors. Networking activities between this industrialization hub, the country's largest UCB bank, the placenta bank, and the IH have yielded both wealth and fame. Han has long-term international collaborations with laboratories in France and with Amcell, and occupies important national positions as regulator, as academician, as 'father of family banking in China', as one of the initiators of a licensed UCB bank, and as advocate of research ethics.

The regulatory orientation of elite institutions that are embedded in private- and state-industrial organizations tends to be multiple, whereby international, state, and commercial requirements are taken into account in industrial decision-making. State elite laboratories that advocate 'international' procedures question the standards of the MSC cells banked used in commercial clinical applications. In their view, only transparency can lead to harmonized standards, which they regard essential to safeguarding their own reputation (interview Hou). But the dense interlacing of powerful state and commercial institutions can be a challenge to regulatory oversight. Furthermore, clamping down on such bionetworks may affect the academic research and industrial services of others, including those of the state itself, as state institutions can benefit from the resources provided by these bionetworks, including biomaterials, bio-banking, and processing services.

2.3 The military and stem cell activities: a separate world

Although China has a diverse network of military hospitals and research institutes, which can be found in all major Chinese cities, as one category, they constitute a different world from other medical institutions because they follow their own regulatory guidelines. Together with university hospitals, military hospitals are seen as the best medical facilities in China. But military hospitals have their own set of rules and regulations for clinical stem cell procedures, and are overseen by military bodies—separate from the MoH—which answer to the Central Military Commission. Military research institutes providing stem cell therapies that are not authorized by the CFDA include the Academies of Military Medical Sciences (AMMS), which offers a cure for diabetes (AMMS 2014), and Peoples' Liberation Army (PLA) universities, such as military and police hospitals, PLA hospitals (Shizhentang 2014), navy

hospitals (Intec 2014), and armed forces hospitals (B&D 2014; Sinostemcells 2015). Its simultaneous closeness to and regulatory isolation from the state has given the military advantages above other stem cell enterprises. Despite the new draft regulation of 2015, military hospitals can continue to provide unauthorized treatment through arrangement they have with small private clinics, which continue to operate. The clinics operate on a hospital's premises and under its licence (Song 2011; Jourdan 2016).

The military hospitals were early providers of stem cell interventions. According to An Yihua, director of the stem cell transplant department at Beijing's General Hospital of the Chinese People's Armed Police Forces, Chinese hospitals have been using foetal brain cells to treat patients since the 1980s. An's hospital alone has treated nearly 4,000 patients with neural stem cells since 2003, including foreign patients from twenty countries (Tam 2011a). Many small hospitals followed suit. Top tier military hospitals, though relatively autonomous from regulatory point of view, collaborate also with international contract research organizations (CROs) in multicentre clinical trials, such as the collaborative study of a Phase I/II ischaemic stroke trial by Neuralstem and BaYi Brain Hospital (Neuralstem 2014), and with hospitals and research institutes at home. Both CAMS and AMMS have close research links with the military hospitals to further translational research. In addition to state research institutions, there are also private research centres and hospitals that collaborate with the military by providing cell-processing services (interview Dan).

In China, the military has a good name among much of the population. The mother of a patient, Zhou was told that stem cells were like seeds; after being planted on a liver, they grow, divide and spread, and finally form a healthy liver. The failure of the intervention was published widely and damaged trust relations (Tam 2011a). Leading translational stem cell researchers interviewed, including scientists from CAMS, regard the stem cells derived from healthy aborted fetuses as an obvious advantage for China's research community. The MoH is aware of this. The military provides therapies to study their efficacy rather than to earn profits. As such, the publication of research results at home is thought to be invaluable as a source of experience with stem cell procedures and as a basis for making research progress.

The military, due to their exceptional status, have remained well-financed and well-resourced closed pockets for research and the provision of what is known as experimental stem cell interventions. They have developed their own regulatory orientation. Their regulatory orientation is rather varied, but the permissiveness of some permits applications disallowed elsewhere in China. Despite the January 2012 Notification (MoH 2012), the military continued to collaborate with both private hospitals and prestigious academic research institutions such as CAS, providing them with access to patients at least until our visit later in the autumn of that year. Although provision is continuing through private clinics, it is not yet clear to what extent the autonomous regulatory orientation of the military networks is being affected by the 2015 draft regulation.

2.4 Beike biotech: cell banking and processing without observing standards?

Beike Biotechnology was set up in July 2005 by Xiang (Sean) Hu in Shenzhen. It was initially concentrated on the development and commercialization of adult stem cell therapies that have been severely criticized for the commercial provision of unapproved stem cell interventions (McMahon 2014). But Beike strategically

deployed international standards for biobanking, scientific research, safety, efficacy, and ethics to maintain its large network.

After his PhD and research on biochemistry and molecular biology at the Universities of Gothenburg (Sweden) and British Columbia (Canada), Hu returned to Zhengzhou University in China in 2001, where he decided to focus on translational research for severely disabled patients. Hu soon attracted capital from Hong Kong Science & Technology and Qinghua Universities (Khayashar 2007). In 2006, the Shenzhen government invested 900k RMB (US\$4m) into its industrial zone, to which it invited Beike, and, in 2009, Beike opened its Stem Cell RM Industrial Complex in Taizhou, calling it 'the world's largest stem cell storage and processing facility' (Beike 2014c).

Beike's work in 2010 with Drum Tower Hospital and Jiangsu University exemplifies its collaborations in translational research and clinical stem cell applications (interview Deng) (Beike 2014b). Financed by Jiangsu Province (US\$1.8 million), the collaboration aimed to develop clinical applications using hUC-MSC to treat systemic lupus erythematosus (SLE), multiple sclerosis (MS), and other degenerative diseases. Beike provided the facilities, equipment, management framework, and certain proprietary clinical stem cell technologies for the project. Nanjing University Medical School's Drum Tower Hospital was responsible for administering the human trials, enlisting 200 patients, while Jiangsu University brought its biological research and development resources to the production and animal study phases of the project (Sun et al. 2010).

Internationally, Beike has also branched out to Bangkok, Delhi, and Malaysia, and it created a rehabilitation centre in Romania and invested in stem cell ventures in Japan and Brazil (Beike 2014a). Beike organizes international conferences, fostering national and international collaborations (Zeng 2009), and maintains connections with political leadership. In 2010, Premier Wen Jiabao and President Hu Jintao visited Shenzhen, where they lauded Beike as 'the world's most advanced venture', although the therapies it facilitates have been prohibited since May 2009 (Youtube 2009). Beike has been criticized for selling 'unproven stem cell therapies' for high fees (60–150k RMB, 2012). In 2013, Beike claimed to have treated over 15,000 patients, of which just over half are Chinese (interview Tu). Revenue is mainly pumped into the company's biobanking branch, which since 2012 has AABB accreditation and collaborative agreements with provincial hospitals on tissue-bank management (interview Yan).

Collaboration with local funders, well-known researchers and hospitals is crucial to Beike's development of stem cell products provided through collaborations with provincial hospitals, while industrial areas, universities, and funders are crucial for its biobanking activities. Its international accreditation and proprietary technologies have gained Beike credibility, and its research and publications have helped Beike to build up experience and academic capital. As Beike's activities are intertwined with state funding, research and banking, provincial funders, universities, and hospitals, it has considerable leverage, which it uses to lobby with the committee formulating the 2015 regulation (personal communication, Yang).

Beike has developed various orientations towards regulation. Although Beike has claimed to adhere to national and international regulations, for a long time it has evaded them by delegating the application of controversial clinical procedures to hospitals, which carry the risks of regulatory violation. On the other hand, Beike has also been developing its own standards for deciding which patients to treat and for measuring treatment progress. In this sense, it has its own regulatory orientation to which it adheres when it can.

Although Beike is best known for its stem cell banking and processing activities, there are other similar industrial networks in operation, such as the ‘Strategic Alliance for Huaxia Stem Cell Industry and Technological Innovation’.¹

2.5 The Guangzhou Alliance: university–hospital–industry alliances

The Guangzhou Alliance exemplifies one of the various university–hospital–industry alliances that aim to translate RM into clinical applications, rather than making profit. Other examples of local alliances, financially supported by local industry, have been set up in Shanghai and Shenzhen. On 19 June 2008, twelve research institutes, hospitals, and companies involved in RM in the Guangzhou area forged a collaboration to set up the Guangzhou and RM Alliance to facilitate clinical applications (Guangzhou Shengwu-Yiyaowang 2014). This bionetwork illustrates how it has been possible for a regional organization to formulate its own standards for safety, efficacy, scientific protocols, and ethics. Six stem cell science institutes in Guangzhou started developing clinical applications for the Guangzhou City Large S&T Expert Program (Guangzhou Shengwu-Yiyaowang 2014). The Alliance, headed by Professor Pei Duanqing from the Guangzhou Institute for Biomedicine and Health (GIBH), aimed, first, to further basic stem cell science, technological innovation, and design industrialization strategies, second, to provide technological training, contribute technical equipment to Guangzhou’s development and sharing of resources, and, third, to develop clinical stem cell procedures.

One example is the collaboration of a tissue-engineering centre (TEC) with various hospitals in transplanting MSCs into thirty patients with GvHD, whereby twenty-two of them clearly showed progress (Guangzhou Shengwu-Yiyaowang 2014). Although the TEC received funding from the Ministry of Education for basic stem cell research in 2007, it also received funding from the local government in Guangdong for translational research. In 2000, the research team found that administering BM-MSCs to rats decreases immunological rejection in GvHD, compared to transplantation of BM alone (interview Deng). Until hearing about a Japanese researcher using a mother’s BM-MSCs for her child’s GvHD, and about Osiris conducting clinical trials on GvHD, the TEC team leader had not planned to clinically apply MSCs. As his university did not have enough funding for clinical trials, and as the funding from local government was only sufficient for clinical studies, TEC started collaborating with hospitals from the Alliance with small amounts of funding, initially for 2–3 years. They planned to apply for a state license after the basics had been put in place. To the team leader, this research was not about making money, but about ‘returning the favor to the taxpayer’ (interview Deng).

The Alliance’s labour division stipulated that GIBH provides the technology, two women’s hospitals provide biomaterials, the Centre for Cells and Tissue Engineering, Southern Medical University, Guangdong Province People’s Hospital, the Third Affiliated Hospital of the Guangzhou Medical Academy, and Guangzhou City’s First People’s Hospital provide the clinical research basis, while Hanshi, Seer, and Guangzhou Huanhuang S&T Companies commercialize it. The Alliance had established its own rules for conducting research and clinical translation to accommodate patients’ demands and fulfil expectations local investors in stem cell applications. The Alliance used the following procedure: researchers had to apply for the permission of IRBs before starting clinical research, and register the research with the Guangzhou Hygiene Department.

After experimental stem cell research was denounced in May 2009, the Alliance started to invite SFDA staff as visiting professors to learn how to conform to the ever-changing standards and regulations, and to coordinate its activities with the SFDA. This would facilitate future applications for marketing licenses (interview Deng).

To facilitate clinical stem cell applications with the support of local governments, the regional alliance developed alternative regulation, formulating its own standards for safety, efficacy, scientific protocols, and ethics. However, after the promulgation of the 2009 *Management Measures for the Clinical Use of Medical Technologies*, it claims to have followed the official line. After the publication of the 2015 draft regulation, alliance research institutions have started to operate on certified hospital premises, as registered experimental interventions can be used as last resort treatment (CFDA 2015; Rosemann and Sleeboom-Faulkner 2016). However, local governments still exert funding pressures to encourage the provision of stem cell interventions for GvHD and to start clinical trials.

2.6 Partly state-dependent enterprises from Changsha: in anticipation of guidelines

The last case exemplifies a semi-private bionetwork that has close links to the state, even though it operates largely independently. Semi-independent research institutions that do not have access to powerful central or regional institutions depend on the state emphasis that their activities follow state rules. Xiangya Reproductive Hospital’s biomedical research in Changsha also shows preparedness to cooperate in forging official guidelines and it is known for its provision of training courses, ethics activities, and charity. The enterprise goes back three generations: Lu Guangxiu, its current leader, followed in her father’s footsteps, and her son followed in hers. In 1984, she opened China’s first *in vitro* fertilization (IVF) clinic, and in 2003, she became President of the Institute of Reproduction & Stem Cell Engineering (Central South University) and President of the Reproductive & Genetic Hospital CITIC-Xiangya. CITIC (China International Trust and Investment Corporation) funded the initial commercialization of the research.

In 2004, the National Development and Reform Commission decided to fund a second national centre for stem cells, the National Centre for Human Stem Cell Research Engineering (NC-SCRE) in Changsha, and asked Professor Lu to lead it. The committee invested 20 m RMB, while Lu had to raise an additional 90 m RMB, which was partly provided by the Changsha local and Hunan Provincial governments (Interview Li, 5 November 2012). In 2009, Lu formed an enterprise, the Hunan Guangxiu Biological Science Co., Ltd. to build the National Centre and the Hunan Guangxiu Hospital next door. The case of Lu’s ‘family enterprise’ illustrates that those conforming to official guidelines change the direction of their research efforts to basic research, but hope to benefit from state support in the future.

Apart from the clinically graded embryonic stem cell bank, CITIC-Xiangya and the NC-SCRE have an umbilical cord bank, a cord blood bank, a placenta bank, and an induced pluripotent stem cell (iPS) bank. Preparations for the cord blood bank started in 2008. Although they have both a private and a public UCB bank, they now want to focus on the public bank to develop clinical stem cell interventions for patients with cerebral palsy, spinal cord injury, ischaemia (for diabetes), cirrhosis of the liver, and pancreatitis. The head of the UCB emphasized that no clinical applications had yet

been made: 'Patients keep ringing to ask for help. But it would be a violation of state regulation, and we have no evidence for safety yet' (interview Shang). Lu and her team were the first researchers to engage with and publish on bioethics issues in practice. As soon as the new regulation is promulgated, the Changsha group hopes to receive funding for their UCB projects. Among their contacts in Beijing are Zhao Chunhua, who had permission to use BM-MSCs and Wu Zuke, a famous academician from AMMS, who works with military hospitals (interview Li). While Zhao and Wu continue their research, Changsha is waiting for the green light.

Although largely independent, this Changsha-based research hub, like other state-dependent institutions engaged in clinical research, needs the support and funding of regulators and potential collaborators in Beijing (CAMS/PUMC) to continue their clinical and research activities. Ethics and research authorization are crucial to their ability to conduct business and to their general credibility. Accordingly, they are keen to follow official guidelines and regulations; to them, regulatory deficit hampers translational research activities.

3. Discussion: diverging regulatory orientations and regulatory capacity building

Global hegemonic pressures have lead governments to follow international guidelines that may not suit a majority of interest groups at home (Sleeboom-Faulkner et al. 2016). In China, initial regulatory reform aimed at policing and enabling the field of clinical stem cell applications in accordance with international guidelines has clashed with the interests of pre-established communities of practice. This led to a prolonged regulatory stalemate, hampering further efforts of national harmonization. The conditions that allowed this development to occur in the first place were related to China's geographical and political characteristics as a large LMIC. Its policy of economic growth whereby 'some may get rich first' (Deng Xiaoping cited by Wong 2014) has created the conditions for uneven and unequal socio-economic and scientific infrastructures. The accompanying diversity in regulatory orientations is characterized by contradictory developments between the political centre and peripheral governing institutions.

The six bionetworks of clinical stem cell research, on the one hand, exemplify the variety of shared and diverging regulatory orientations in agreement with these socio-economic inequalities and contradictions, and, on the other hand, reflect the frictions between dominant global regulatory trends and the development of local regulatory arrangements. The development of locally entrenched bionetworks with their particular communities of practice has made the creation of an effective national regulatory infrastructure a major challenge. Local bionetworks have invested in material and intellectual resources, patient recruitment, research networks, commercial relations, and collaborative agreements with municipal, provincial, and national governments over a sustained period of time. They display a range of regulatory orientations in terms of setting standards for safety, efficacy, scientific protocol, licensing and ethics, shaped variously through local, regional, public, private, and state institutions (see Table 2).

One of the reasons that make it hard to change the ways in which clinical stem cell research is practiced in China is their embedding in bionetworks, which feed on local power structures, and the cross-linkages between the bionetworks. Although bionetworks operate around the norms and rules shaped by a shared

organizational orientation and scientific practice, they are also tied with other bionetworks with different scientific norms and regulations. These cross-cutting linkages can be found between bionetworks across China and beyond. Thus, we saw that Hanshi in Tianjin was a member of the Guangzhou alliance, Beijing's CAMS operated a biobank with Tianjin's IH; Changsha works closely with Beijing's PUMC, CAMS, but also Lu Daopei hospital, which works closely with military hospitals (interview Dan); and, besides having links to the cord blood banks of various provincial capitals, Beike has close links with Sun Yat-Sen University in Guangzhou. Some bionetworks have myriad collaborations with research institutions abroad, which may well thrive due to differences in the permissiveness of national regulatory systems (Sleeboom-Faulkner and Patra 2011). Standards for clinical stem cell applications co-developed by local investors, researchers, and the stem cell industry diverge from official guidelines, and the promulgation of the 2015 draft regulation promised to eliminate these inconsistencies.

3.1 Regulatory implications

The implementation of the new draft regulations is likely to reconfigure the position and the regulatory orientations of bionetworks. It is bound to result in unequal access to financial resources, including state funding and industrial investment. Elite institutions are likely to benefit, but the new standards and requirements may be unaffordable to those less well-resourced or without state support. Although the new draft regulation is clear about its requirements for clinical trials, it is not so about the specification of stem cell lines and the future of clinical stem cell research outside the new regulatory framework. It is unclear whether the clinical use of stem cells will be permitted for patients without other options and under what conditions. The Guangzhou Alliance, Beike and Hanshi (interviews Deng; Tu; Cai), as well as some elite institutes (interviews Li; Dan) considered such experimental treatments justified as a last resort option, and all researchers emphasized the pressure exerted by local funders and patients to develop 'therapies'. On the basis of former trends, it is likely that the provinces and municipalities that have their particular vested interests in patient health and clinical stem cell products will interpret the draft regulation in a manner that befits established investment patterns for clinical applications.

Considering that the various bionetworks have developed procedural standards that cater to their own particular 'technological zones', it is not surprising that the national government has been struggling to articulate a set of regulations acceptable to all players. The 2015 draft regulation has foremost accommodated the regulatory demands of elite laboratories. However, the requirements for market approval for clinical trials and the conditions for routine use of pharmaceutical stem cell products in hospitals have not been published (Sleeboom-Faulkner 2016). The 2015 regulation no longer speaks of controlled research trials (Phases I–III) (MoST 2013), leaving open the possibility of adopting a Japanese or South Korean model that allows conditional market approval on the basis of clinical studies with relatively small numbers of patients (Azuma 2015). In any case, considering China's diversity of bionetworks and large number of medical institutions, a successful implementation of the draft regulation will require considerable investment in regulatory oversight.

It is not clear how the regulation affects clinical stem cell practices of the army and police hospitals, where many commercial stem cell activities have been located in recent years. As the army and police hospitals conduct a large proportion of clinical stem cell

Table 2. Bionetworks, socio-economic and political conditions, and their regulatory orientations

Bionetworks	Socio-economic and political conditions	Regulatory orientation
1. Elite institutions close to main regulatory power hubs (Example CAMS, Beijing)	As close to state power, has favourable access to state funding; is respected; has say in creating guidelines; under the state's aegis; internationally respected; collaborates with private companies and the military	Positive regulatory orientation, guidelines are advantageous, and as under close state control. Pioneer <i>authorized</i> clinical trials and research. When formal regulatory defunct, it may receive special permissions to continue supervised activities.
2. Stem cell industries straddling elite research institutes and private companies (Example Tianjin)	Funding access to the state, industry and investment; for-profit stem cell service provision; regional government support; international clout	Multiple regulatory orientation, depending on the collaborative partner concerned; provides ' <i>unproven</i> ' stem cell interventions <i>commercially</i>
3. The military stem cell hubs	Plentiful funding and resources; large available patient pool; trusted by the public and respected all-round; collaborates with private companies and state research institutions	Independent regulatory orientation, independent from state interference (until 2015); major provider of ' <i>unproven</i> ' stem cell interventions and conducts clinical trials
4. Large-scale commercial cell banking and processing industry (example Beike Biotech)	Lucrative industry providing patients with cell-related services, which are ministered by collaborating hospitals; have close ties and collaboration with local governments and a number of universities, jointly conducting clinical trials.	Double regulatory orientation that tends to evade state guidelines and regulation when possible, emphasizing bioethical principles such as informed consent, patients' self-reporting, patient numbers, and <i>high technical standards</i> , e.g. for banking.
5. Regional university-hospital-industry alliances away from Beijing (example Guangzhou)	Receive regional funding (from local governments, industry) to translate RM into clinical applications to cater for the growing demands for RM. Often relatively isolated from Beijing regulators and power.	Split regulatory orientation. When possible, adhere to collectively developed guidelines influenced by international precepts and local needs, but when pushed follow official guidelines.
6. Enterprises partly dependent on the (distant) state—partly privatized (example Xiangya, Changsha)	Partly dependent on state-funding and partly dependent on own/industrial funding. At a distance from Beijing, needs toeing the official line to sustain itself and linked enterprises.	Its compliant regulatory orientation is following, supporting, and advocating the official line. When state regulation is defunct, activities in the area concerned are hampered.

research in China, this may affect the overall development of the field. Furthermore, it is uncertain to what extent the new regulation can be ignored or circumvented. The new regulatory arrangements provide official permission for clinical applications only to the stem cell trials that take place in qualified hospitals. Although the draft regulation allows clamp down on unauthorized stem cell applications (McMahon 2014), its focus on review could leave China's trade in stem cell products unmonitored (Rosemann and Sleebloom-Faulkner 2016). The new draft regulation also leaves open questions about the international collaboration stem cell community hope to maintain. The emphasis of the regulation on preclinical studies, clinical trials, quality controls, and independent expert committees corresponds with guidelines developed by the ISSCR (ISSCR 2008), US Food and Drug Administration (US-FDA 2015) and European Medicines Agency (EMA 2007), but clarity on the conditions for market permissions, IPR, and the role of foreign research entities in collaborative research are crucial to attract investors and collaborative partners.

Conclusion

This article began by asking why in China national regulation took a long time to develop and, even under the 2015 draft regulation, is still unclear in crucial areas. Rather than just referring to theories that emphasize the debilitating influence of the hegemony of 'Western' stem cell regulation, or concentrating on the ways in which the government may have tried to enable China's varied landscape of clinical stem cell research to develop, we have outlined some of the difficulties of regulatory steering in China as a

large LMIC. Apart from being subject to international political and regulatory trends, we showed how the development of procedural standards is complicated by the existence of bionetworks with shared and diverging regulatory orientations. These orientations were shaped in interaction with international, national and provincial governments and local policies financial, economic, and regulatory policies.

Although any country's institutional landscape of clinical stem cell research may be varied, in China this variety has been allowed to flourish and to consolidate through local bionetworks—entrepreneurial scientific networks that share particular scientific norms and practices—for a sustained period of time. The initial, only partly implemented, regulatory conditions in this complex landscape have made it possible for a large number of researchers in China to forge ahead in the clinical stem cell field through unauthorized clinical applications. Nevertheless, already before 2009, the number of stem cell scientists calling for tightly controlled regulation had started to grow; these voices wanted China to take a legitimate position in the global clinical stem cell research field. In this sense, China is an *old* newcomer: its size, the state's ability to fund state-of-the-art stem cell science, its varied institutional landscape and its 'permissive' regulation (Sleebloom-Faulkner and Patra 2009) had made China an early starter in the field.

The 2009 regulation was a first visible effort to control and regulate the field by the official announcement of the intention to clamp down on for-profit human stem cell enterprises, a step which started to have perceptible effect only since 2012. Although the initial development of the stem cell field had benefited from the relatively uncontrolled environment with its diverse range of stem cell

networks, it has increasingly become a hindrance to the field's growing cosmopolitanization (Zhang 2012). Thus, the international compatibility of research standards, reputation, and ethics became essential to China's elite centres' efforts to merge with technological zones evolving in the clinical stem cell field, while other bionetworks developed their own idiosyncratic arrangements in line with the aims of local investors and incidental national and international projects. The true challenge China is facing is the double-edged sword of regulatory capacity building: to create national regulation acknowledged by potential collaborators at home and abroad, as well as to cater for the various bionetworks with the potential to fulfil China's political strategy as world leader in the field of stem cell science.

For this reason, we argue that the notion of regulatory capacity building must not indicate the importation of guidelines from other organizations or countries. Rather, it needs to refer to the ability of a country to relate to scientific communities that have been formed under different conditions. The notion of regulatory capacity building, then, needs to refer to the capacity to develop regulation that deal with the regulatory discrepancies between international and national guidelines, and the different regulatory orientations among local bionetworks. This means that the implementation of regulation should have enough clout to function as planned in transactions and in exchanges with both institutions abroad and at home, while being flexible enough to adapt if implementation is impeded at home. In China, such efforts are complicated by the entrenched financial and research interests and regulatory orientations that are embedded in the various bionetworks, some of which cater to the demands by Chinese as well as international patients, and others of which have unauthorized arrangements with powerful (legitimate) research institutions. On an international level, this means that, to avoid clashes as a result of global regulatory discrepancies, the development of new regulation needs to be more inclusive of researchers in large LMICs such as China.

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Note

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Appendix: Interview references

Table A.1. Interviewees

Pseudonym	Location	Date
Cha	Beijing	17 May 2007
Cai	Beijing	28 October 2012
Dan	Beijing	30 November 2012
Deng	Guangzhou	25 April 2013
Hou	Tianjin	17 October 2012
Li	Beijing	23 November 2012
Lie	Changsha	5 November 2012
Shang	Changsha	6 November 2012
Tu	Shenzhen	22 April 2013
Yan	Taizhou	29 June 2012
Yang	Shanghai	20 June 2014